ABOUT CPT-11 (CAMPTO™)

Differences between topoisomerase 1 metabolism among mice and men

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Several human clinical studies are currently being carried on concerning a topoisomerase 1 inhibitor, CPT-11 or Campto™, following "encouraging" preliminary trials on mice. The purpose of this note is to call attention on the fact that these trials do not seem to be extendable to man, in view of an agonism that one can predict for man, but not for mice, between topoisomerase 1 and a recently discovered angiogenesis inhibitor, angiostatin; leading one to anticipate in the majority of cases a worsening of angiogenesis in case of use of this drug on man. We thus recommend an immediate cease of these experiments.

As we have described in other papers[1], the scale resonance effects associated to protein biosynthesis allow one to predict, through the epigenetic regulation they exert on it, their metabolic agonisms and antagonisms from the data of their amino-acid sequence, by examining the corresponding quantum frequencies. Labeling 0 to 9 the ten distinct frequencies which remain associated to amino acids after they get fixed onto their transfer RNA, one observes a good dozen homologies between the 300 first amino acids of topoisomerase 1 and the sequence of angiostatin, an important inhibitor of angiogenesis:

Human DNA topoisomerase 1 (above in brackets: mouse)

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52046464425451478444265654565485686556555548552562425654255 5
""""   ''''     '''''              +++++

655555356540225565456548455585555381204154555554072233545453
   ******
     (1)          (4)   (1)
5440873335544534583845443485355453543555558545555405455354 54
     ~~~~~~~~~~   ~~~~   ~~~~

    (1)
5455335344555535555555959955588350459574565033713385343543 57
 ******       ---------- °°°°°°°°°
8840535542351553137715544658335547854775498555345554443442 53
                          ■■■■■■■
4735525875153518555255554545554554455807345446558414754533 04
7808046355054588453544444325415332333065955386445339432935 44
5024584544322845055495585318845533454845885495255553858131 48
                                                      (3)
7445414810455550531433033248356444635440558335747405424888 45
                                                       """""

3335583754454755455354447484430444564544550431537838412434 55
5455431345443154428481481314434658133537552554453544154155 54 14
1884452151415355415355333525551358455545545351348554554140 325
4484438433193559033455484535855719144514548 57
```

Human Angiostatin (homologies of successive quantum frequencies with topoisomerase 1 are underlined by identical typographic characters; above in brackets: mouse)

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                                (1)
5384253530405488035253540433559223236838723136325045548384 34
  ''''                          -----

                                      (8)     (5)
44350393833435588483444535553563205484054253520453519425236 1
                                  ******      """""  """"
                        (6) (0)
6084325734544554838434854839373343458954344383333332203385 34
       ~~ ~~~~~ ~~~~~~~~
                                                    (5)
503054880431333206335692153363648335473354445483843405813936
                                        ######^^^^^^^ ^^^^^^
                                              ~
33425389583543234223323554133133543333543860405288032233330 5
       °°°°°
              (2)                                                  (8)
535292253368655335483410435483843414503937334323895834455 3
          ++++++***          ~~~~~~                    °°°°*****
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This leads one to predict a strong metabolic agonism between those two proteins, and as a consequence that an inhibition of the former would reflect on the latter, thus des-inhibiting angiogenesis. On the contrary, most of these homologies (9 out of 12, among which the most significant ones underlined by +, * et ~) disappear in the case of the mouse sequences (8 on angiostatin's side[2], 5 on topoisomerase 1 side, 4 on both sides together); from which follows that the results observed there cannot be extended to man.

This has particularly severe consequences when the other regulatory pathways of angiogenesis are themselves invalidated, the thrombomodulin way through a mutation of p53 and the platelet factor 4 way through a mutation of platelet-derived growth factor β; which would necessitate at the very least a molecular oncogenic analysis before experimenting, so that we can only recommend an immediate cease of these experimentations under present circumstances.

In addition, coming after a similar observation concerning the *ob* gene product leptin[3], this strengthens the necessity that the implications of homologies of successive frequencies associated to protein biosyntheses be taken into account before undertaking any study of this kind.

(1) J. Sternheimer, *Scaling waves*, seminars given at the European University of Research (Paris), 1994-1995; *Method for epigenetic regulation of protein synthesis by scale resonance*, patent n° FR 92 06765 (1992), U. S. patent application n° SN 08/347.353; *Application des homologies de suites de fréquences de la troponine C à la prédiction de son métabolisme*, preprint (1995); *Régulation épigénétique de la biosynthèse des protéines et prédiction de leur métabolisme à partir de leur séquence*, preprint (1995).

(2) M. S. O'Reilly *et al.*, *Angiostatin: a circulating endothelial inhibitior that suppresses angiogenesis and tumor growth*, Cold Spring Harbor Symp. LIX, p. 471 (1994); Cell 79, p. 315 (1994).

(3) J. Sternheimer, *Sur les différences métaboliques de la leptine (produit du gène ob) chez la souris et chez l'homme*, preprint European University of Research (1995).